Inhibitory interneurons of macaque primary visual cortex

Kooijmans, R.N.

2016

document version
Publisher's PDF, also known as Version of record

Chapter I

General introduction

The main functional cellular unit of the brain is the neuron (Figure 1.1). Due to its electrically polarized membrane and specialized ionic channels, such a cell is capable of receiving signals from other cells (either depolarizing or hyperpolarizing), generating an action potential, propagating it along the length of its axon, and then relaying this information to another cell. The relay process between two neurons is based, in the classical description, on the conversion of the neuronal electrical signal to a chemical one, at the location of the synaptic cleft. The synapse (Figure 1.2) is a specialized relay space between two communicating neurons, where a presynaptic neuron releases a chemical neurotransmitter that, by binding to specific receptors, will lead to a depolarization (or hyperpolarization) of the postsynaptic neuron, and the generation (or extinction) of an electrical signal in this cell (Kandel et al. 2012).

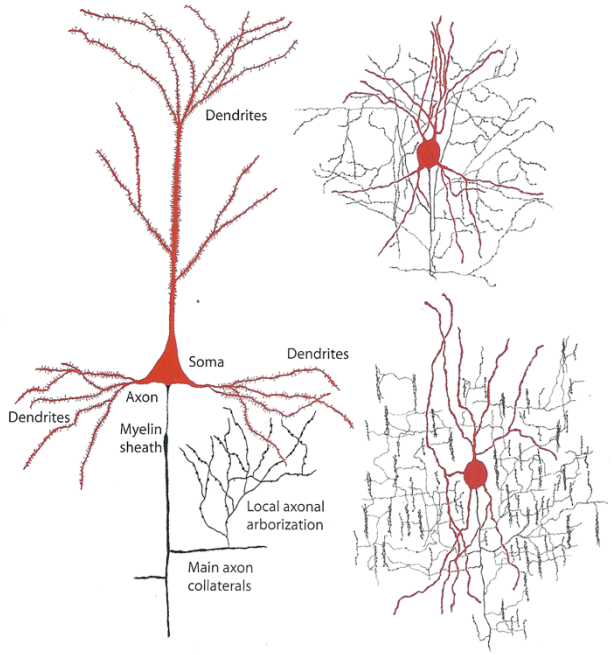

Figure 1.1: Schematic representation of neuronal cells. (A) Typical pyramidal cell. (B) "Common type" interneuron (Ramón y Cajal 1899b). (C) Chandelier cell. The dendrites and somata are shown in red, the axonal arborisations in black. Modified from DeFelipe (2010 p.12).

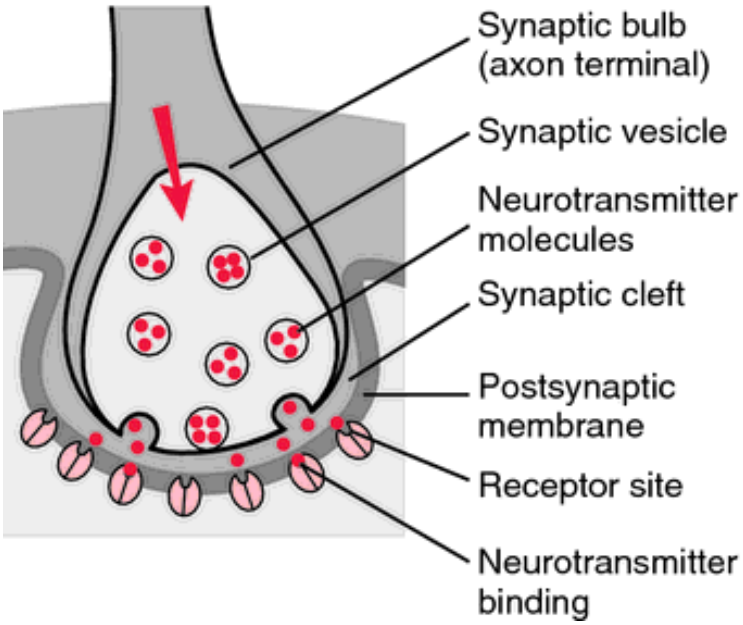

Figure 1.2: Schematic representation of the synaptic relay between two neurons. Modified from Applegate (2000 p.176).

A presynaptic cell that elicits depolarization in a postsynaptic cell is an excitatory neuron, because it leads to the generation of activity in the cell it targets. Excitatory neurons are dominant in the nervous system, and were the first, and most extensively characterized, and modelled (Curtis and Cole 1938; Cole and Curtis 1939, 1941; Hodgkin and Katz 1949; Shanes 1949; Bullock and Hagiwara 1957).

A presynaptic cell that leads to the hyperpolarization of the postsynaptic membrane is an inhibitory neuron. Inhibitory neurons play a crucial role in controlling the activity of the cortical network (Horridge 1968; Isaacson and Scanziani 2011; Fino et al. 2013). In the primary visual cortex, by suppressing activity of other neurons, inhibitory interneurons determine the tuning of excitatory neurons, they contribute to orientation selectivity and surround suppression (Burkhalter 2008; Isaacson and Scanziani 2011; Adesnik et al. 2012; Li et al. 2012).

There are many types of inhibitory neurons and various schemes for classifying them (Markram et al. 2004; Ascoli et al. 2008; Burkhalter 2008). The current work is aimed at systematizing and clarifying inhibitory neuronal architecture of macaque primary visual cortex (V1).

We explored several anatomical features of inhibitory interneurons together with their functional implications. We believe that the new insights we provide will allow for better modelling and prediction of cortical processing, as well as better translation of rodent models to primate applications.

Mouse v. macaque

The development of therapies for human (primate) in rodent models assumes some degree of equivalence of cortical organization between rodent and primate architecture. To assess this in the context of inhibitory interneurons, we compared the expression of calcium binding proteins (CBPs) in primary visual cortex (V1) of mouse and macaque (Kooijmans et al. in preparation; **Chapter II**).

Labelling based on CBPs – parvalbumin (PV), calbindin (CB) and calretinin (CR) is routinely used for primate interneuronal population identification. In macaque, CBPs label interneurons exhaustively, separating them into largely distinct populations (Kooijmans, Sierhuis et al. in preparation; Van Brederode et al. 1990; Härtig et al. 1996; Pinheiro Botelho et al. 2006; Sherwood et al. 2007; Disney and Aoki 2008; Ma et al. 2013; Kooijmans et al. 2014). CBPs make up an intrinsic classification system, besides a labelling scheme, as they are the same class of molecule and have scalable calcium binding behaviour properties due to the "EF-hand" motif expression, directly relevant for their cellular function (Chard et al. 1993; Lewit-Bentley and Réty 2000; D'Orlando et al. 2002; Schwaller et al. 2002; Grabarek 2006; Barinka and Druga 2010). Unlike the low co-expression of CBPs present macaque (Van Brederode et al. 1990; Härtig et al. 1996; Sherwood et al. 2007), there is significant documented co-expression of CBPs in mouse (Park et al. 2002; Gonchar et al. 2007). As a result, the more efficient labelling system for rodent uses a CBP – PV, a hormone – somatostatin (SST), and the serotonin receptor 5HT3a (Lee et al. 2010; Rudy et al. 2011) for separating largely independent inhibitory interneuronal populations.

There is no direct correspondence between the two labelling schemes,

which makes it difficult to translate mouse data to primate. We checked the cross-species distribution correspondence of the PV-CB-CR labelling scheme, as SST and 5HT3a are suboptimal cell markers in macaque (Hendry, et al. 1984; Campbell et al. 1987; Jakab and Goldman-Rakic 2000; Watakabe, et al. 2009). We compared the two species directly, using antibodies that recognized aminoacid sequences preserved between the two mouse and macaque, and used automated counting methods and objective thresholding of the acquired images. We analysed the expression of CBPs along the depth of the cortex in a continuous manner, to also assess sub-layer patterns of expression (Kooijmans et al. in preparation; **Chapter II)**.

Fig. 12. Erwachsener Mensch. 25 : 1, 10 μ.
Übergangsstelle des Calcarinatypus (↓) wie in Fig. 11. Die Schichten sind die gleichen: rechts die achtschichtige Rinde der Area striata (Feld 17 unserer Hirnkarten), links der sechsschichtige Occipitaltypus der Area occipitalis (Feld 18).

Figure 1.3: Typical layer organization of primary visual area V1 (right of arrow). Modified from Brodmann (1909 p.33).

Primary visual cortex

We focused on primary visual cortex (V1) (Figure 1.3), as it is the morphologically most complex (Brodmann 1909), as well as one of the

most extensively described cortical areas (Ramón y Cajal 1899a; Mai and Paxinos 2011). V1 is the first cortical processing station in the visual processing stream (Figures 1.4 & 1.5). Its layer organization is very distinctive (Figure 1.3), and strongly preserved in primates (Brodmann 1909).

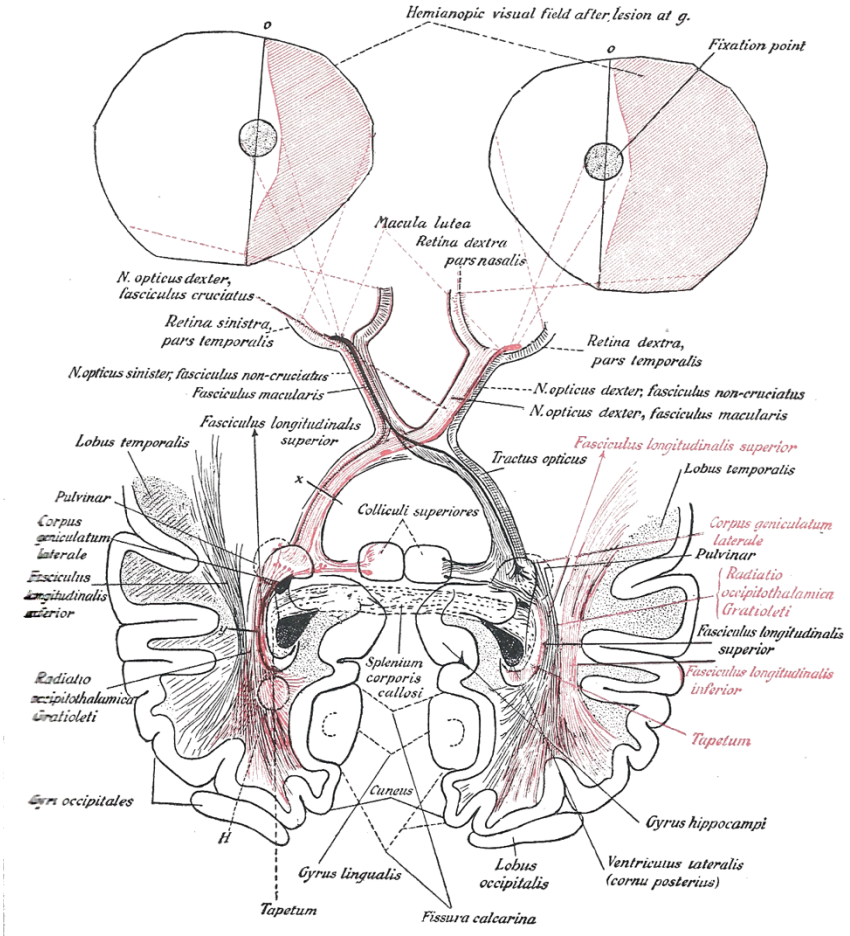

Figure 1.4: The primary visual cortex (along fissura calcarine / the calcarine fissure), as the first cortical procession station in the visual stream. Modified form Barker (1899 p.829).

In primates, the visual system occupies a large portion of the cortical surface, and it is the dominant sensory modality (Witten and Knudsen 2005). The visual system, and V1 in particular, are a benchmark for both anatomical and physiological studies. The shared organizational traits of primary sensory areas, resulting from their similar processing demands,

make V1 data highly relevant for other modalities as well (Mai and Paxinos 2011).

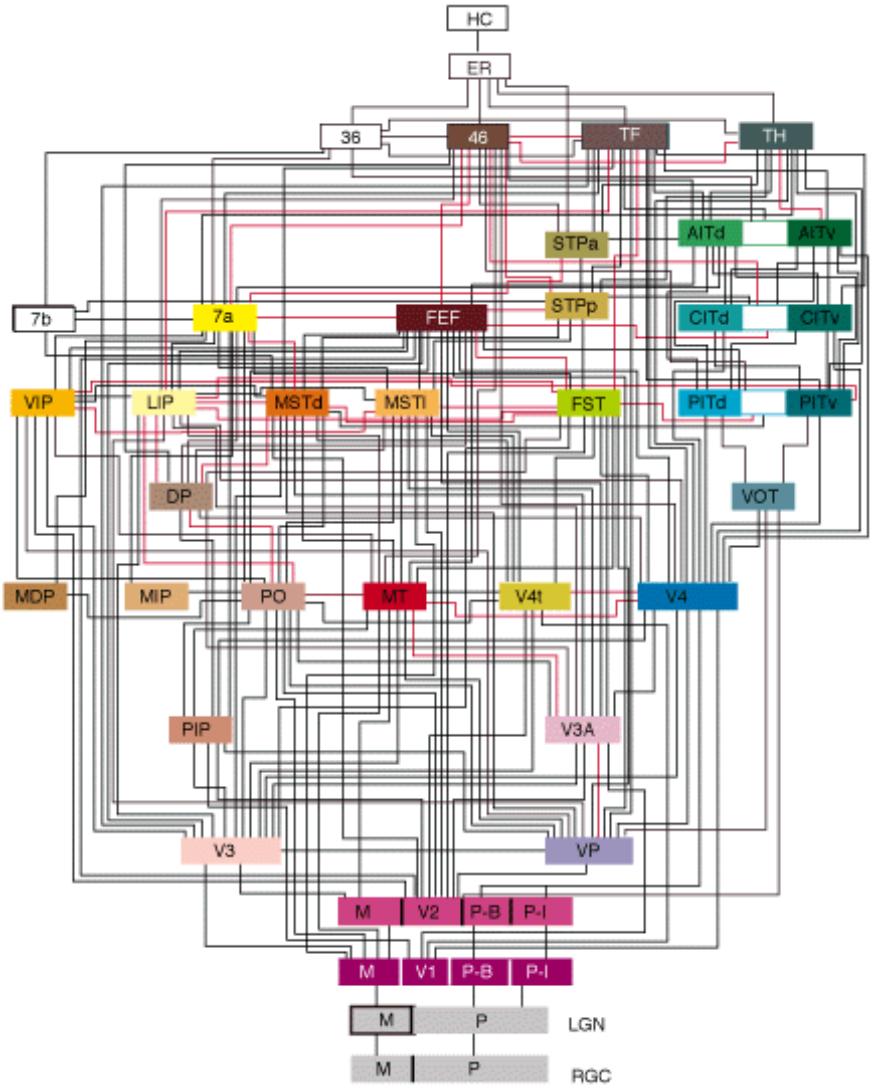

Figure 1.5: Hierarchy of cortical areas in macaque visual processing. Initial information enters hierarchy at the bottom level. Modified from Felleman and Van Essen (1991 p.30).

Feedforward and feedback processing

V1 receives input from the retina via the lateral geniculate nucleus (LGN) (Figures 1.4 & 1.5), and relays it to higher cortical areas involved in visual

processing (Felleman and Van Essen 1991) (Figure 1.5). This type of information processing is labelled feed-forward, as the neural signal flow goes from the receptor in the retina to the LGN, V1, V2, and so forth, to areas that perform increasingly complex computations (Felleman and Van Essen 1991). V1 also receives information from other "higher" cortical areas involved in visual processing. This type of relay is feedback processing, as the transmission of information occurs backwards, from more remote cortical areas to V1. The layers targeted by feedforward and feedback projections to macaque V1 are distinct (Rockland and Pandya 1979; Lund 1988; Rockland 1994).

Feedforward and feedback neural signatures can be differentiated using a figure-ground segregation task (Lamme 1995). This task requires a monkey to identify a figure defined by texture on a differently textured background (Figure 1.6). The figure size for the original task is larger than the receptor fields of recorded V1 neurons, with no predicted difference between a textured figure and a textured background at the level of the V1 receptive field. The time course of the neural signal associated with this task in V1 shows two components, which suggests differential involvement of feedforward and feedback processing (Figure 1.6). The first component is similar for receptive fields located either on a figure or on the ground. This phase of the signal is most likely exclusively driven by feedforward (retina to LGN to V1) detection of texture, in a recorded visual field. The second component of the signal is different for the figure and ground conditions, showing enhanced neuronal activity for the figure, and reduced activity for the ground condition. Due to the smaller-than-figure size of the receptive field recorded, this effect cannot result from feedforward information flow from the retina. This neuronal signature has been attributed to some form of recurrent processing, either lateral (within V1) or feedback (higher areas to V1) (Lamme 1995; Li et al. 2001; Rossi et al. 2001; Li 2003; Self et al. 2012, 2013). Interestingly, the two phases of the figure-ground segregation signal originate in layers of V1 that correspond to feedforward and feedback long-range projections (Rockland and Pandya 1979; Lund 1988; Rockland 1994; Self et al. 2013). They also appear to be associated with distinct oscillatory frequencies that originate in these layers (Van Kerkoerle et al. 2014).

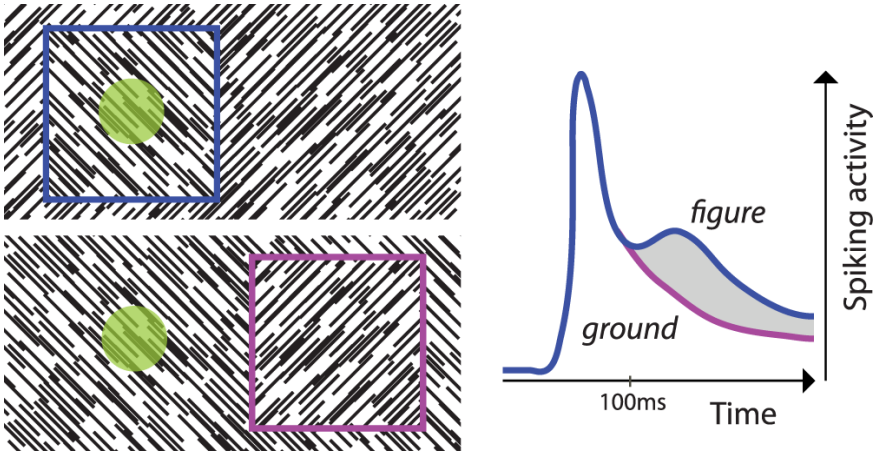

Figure 1.6: The neural correlates of figure-ground assignment in V1. Neurophysiological studies have found that the late (>100ms) spiking activity of neurons in V1 is increased when their receptive field (red circle) is placed on a figure (upper panel, figure outlined for clarity) compared to when they are responding to the background (lower panel), even for identical texture inside the receptive field. This figure–ground modulation (grey region in the right graph), is likely the result of feedback from higher visual areas. Modified from Self et al. (2015 p.2).

Classification of inhibitory interneurons

Neurons can be classified using a variety of criteria, including function, projection target, morphology, and firing behaviour. Functionally, the majority of neurons are excitatory, causing depolarization and potentially leading to an increase in the activity of neurons they target synaptically. The main excitatory neurotransmitter is glutamate (Nieuwenhuys et al. 2007; Kandel et al. 2012). A smaller number of neurons (20-30%) are inhibitory, reducing the activity of interneurons they target, via the neurotransmitter gamma-aminobutyric acid (GABA) (Markram et al. 2004; Isaacson and Scanziani 2011; Luft 2014). A third group consists of modulatory neurons that regulate the function of a group of targeted neurons via diffuse neurotransmitter release, rather than relay signals via synaptic transmission. The cell bodies of neurons belonging to modulatory systems are, however, located in subcortical nuclei (Nieuwenhuys et al. 1998, 2007). As a result, excitatory and inhibitory cell types dominate the neocortical population.

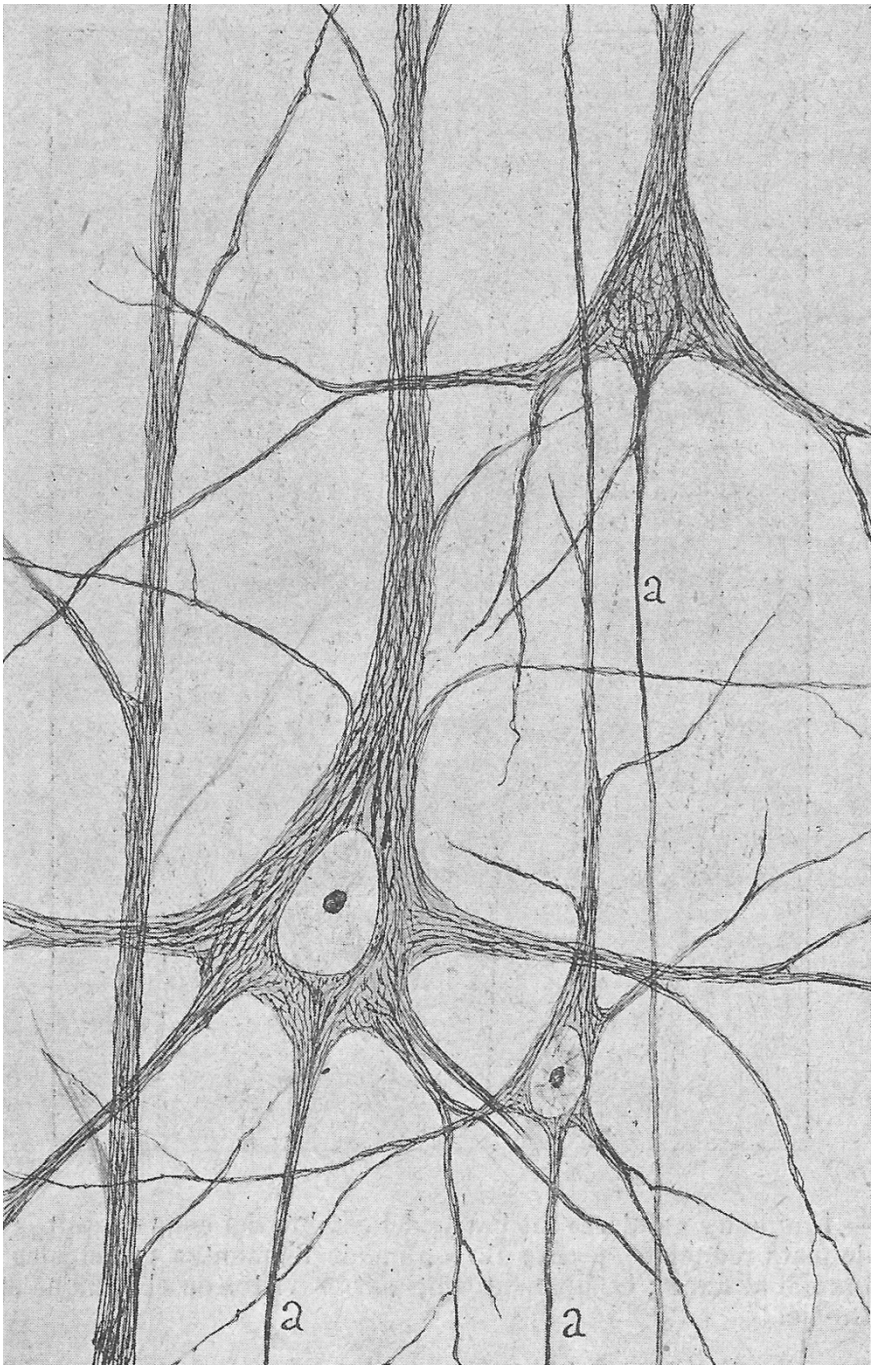

Figure 1.7: Typical morphology of pyramidal cells. Modified from Ramón y Cajal (1904 p.820).

Another way to classify neurons is by the location of their projection target. Neurons that project to other structures, cortical or subcortical, are (long-range) projection neurons. Ramón y Cajal named these "long-axon" neurons (1899b). Neurons that project within the structure where their cell body is located, without their axon leaving the cortex, can be referred to as either local-circuit neurons or interneurons (Ramón y Cajal 1899b; Nieuwenhuys et al. 2007). Ramón y Cajal identified these as "short-axon" cells (1899b).

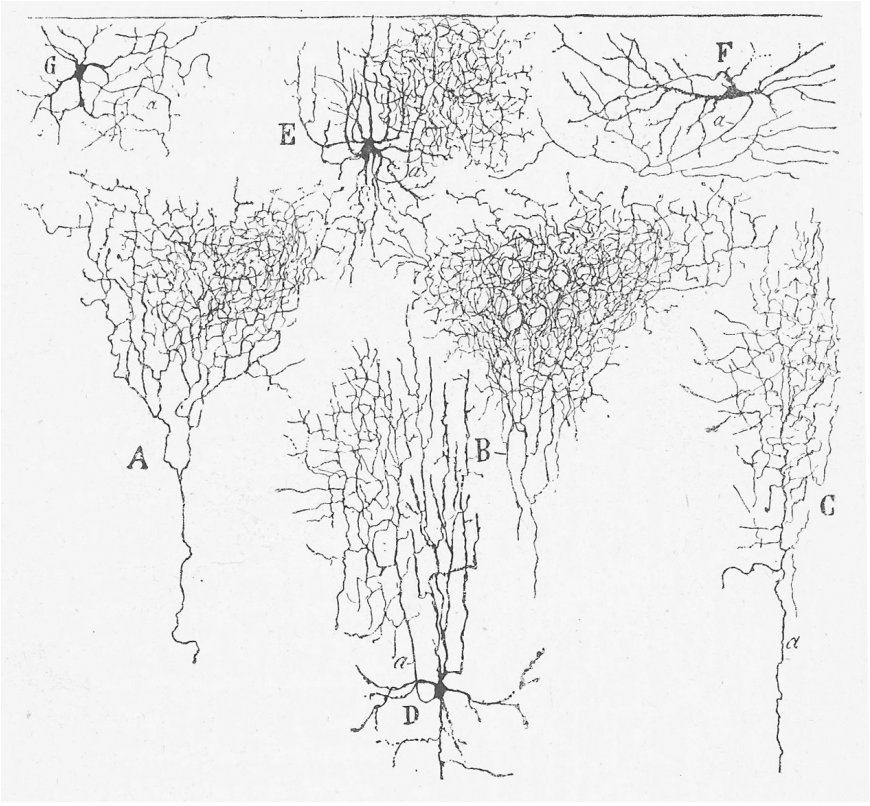

Figure 1.8: Overview of interneuronal morphologies as first documented by S. Ramon y Cajal (1904 p.811).

Morphologically, the vast majority of neurons is pyramidal (Ramón y Cajal 1899b; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007) (Figure 1.7). This applies to most of projection-, as well as local-circuit neurons. The remaining local-circuit morphologies are spiny stellate, neurogliaform, chandelier, basket, nest basket, vertically oriented (bipolar, bitufted, double bouquet), Martinotti, and horizontal (Ramón y Cajal 1899b; Jones 1984;

Kisvárday et al. 1986; Kisvárday et al. 1990; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007; DeFelipe et al. 2013) (Figure 1.8). Of these, only spiny stellate morphologies are excitatory as a rule. Therefore, cortical inhibitory interneuron types, although they constitute a numerical minority, account for the majority of morphological variation.

According to firing behaviour, cortical neurons are either regular spiking, fast spiking, or intermediate spiking. Excitatory neurons are generally regular spiking, while inhibitory interneurons can be either fast spiking or intermediate spiking (Zaitsev et al. 2005; Burkhalter 2008).

Since inhibitory interneurons are a morphologically heterogeneous group (Ramón y Cajal 1904; Lund 1987; Lund et al. 1988; Lund and Yoshioka 1991; Lund and Wu 1997; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007; Burkhalter 2008; Isaacson and Scanziani 2011), much work has been dedicated to further differentiating between different types (Markram et al. 2004; Ascoli et al. 2008; Burkhalter 2008). There are, however, shared traits of inhibitory interneuronal groups in macaque, which divide them into two groups, and correlate with calcium-binding proteins they express. These traits include subcortical progenitor group origin (Ma et al. 2013) and firing patterns (Zaitsev et al. 2005). Such findings suggest that there are underlying commonalities, and possibly more functional cohesion than there is morphological.

Glutamate receptors

Glutamate is the principal excitatory neurotransmitter in the central nervous system (Nieuwenhuys et al. 2007; Kandel et al. 2012), and glutamate receptors mediate the majority of excitatory input to inhibitory interneurons.

A large variety of glutamate receptors (GluRs) introduces additional complexity to synaptic transmission, while binding the same substrate (glutamate). According to impact of substrate, GluRs can be divided into either metabotropic or ionotropic (Dingledine et al. 1999; Kandel et al. 2012; Sherman 2013; Rondard and Pin 2015). Metabotropic receptors

(mGluRs) activate biochemical cascades that lead to the modification of other proteins. There are eight different subunits identified so far, which have been divided into three groups, according to sequence similarity, pharmacology, and transduction mechanism (Pin and Duvoisin 1995; Pin et al. 2003; Kandel et al. 2012; Rondard and Pin 2015). Ionotropic glutamate receptors (iGluRs) are trans-membrane ionic channels that undergo a conformational change following substrate binding, resulting in the flow of ions through the cellular membrane, effectively leading to its depolarization (Dingledine et al. 1999; Kandel et al. 2012). These can be divided into AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate), kainate, and NMDA (N-Methyl-D-aspartate) receptors, according to the alternate agonist substrate they bind (Dingledine et al. 1999; Kandel et al. 2012). In the current work, we concentrated on the expression of AMPARs and NMDARs, as the predominant glutamate receptor classes (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**).

AMPA receptors (AMPARs) are the fast-acting class of glutamate receptors. Four AMPAR-subunits have been characterized, GluA1 through GluA4, which are expressed by excitatory and inhibitory neurons in macaque V1 (Carder and Hendry 1994; Carder 1997). The subunit composition of individual AMPA receptors determines their permeability for sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) ions, with AMPARs containing the GluA2 subunit impermeable for Ca^{2+} (Lerma et al. 1994). Furthermore, different AMPAR subunits play distinct roles in synaptic plasticity (Kessels and Malinow 2009).

NMDA receptors (NMDARs) on the other hand, mediate slow synaptic transmission, and are involved in long-term potentiation and depression (Bliss and Collingridge 1993; Dingledine et al. 1999; Shipton and Paulsen 2014), as well as synaptic integration for discrete dendritic inputs (Larkum et al. 2009). There are three described subunit groups for of the NMDA receptor: GluN1, GluN2 and GluN3. The GluN1 subunit is glycine binding and has eight splice variants (Conti et al. 1997; Köhr 2006). There are no documented spatial or functional particularities of GluN1 splice variants. GluN2 is the only glutamate-binding NMDA subunit and has four documented isoforms A, B, C and D (Standaert et al. 1996;

Dingledine et al. 1999 Küppenbender et al. 2000; Cull-Candy and Leszkiewicz 2004; Clarke and Johnson 2006; Erreger et al. 2007). GluN3 is again a glycine binding subunit, with two isoforms, A and B (Chatterton et al. 2002). Typical NMDA receptors consist of four subunits, most frequently two GluN1 and two GluN2 subunits. The replacement of one GluN2 by a GluN3 is also possible, resulting in reduced the Ca^{2+} permeability of the receptor (Henson et al. 2010). Such subunit configurations require glutamate as an agonist, glycine as a co-agonist. More recent results demonstrate that GluN1 and GluN3 subunits can also form tetrameric receptors which are glycine binding and de facto not glutamate receptors (Chatterton et al. 2002).

Receptor expression and pharmacology

Many basic receptor-mediated synaptic mechanisms such as long-term potentiation (LTP) and long-term depression (LTD) were first demonstrated in excitatory neurons (Siegelbaum and Kandel 1991; Bear and Malenka 1994). The rules governing LTP correlate with glutamate receptor expression, including AMPA to NMDA receptor ratio (Kullmann et al. 2000; Kopec et al. 2006; Rasch et al. 2011), as well as AMPAR and NMDAR subunit composition (Jia et al. 1996; Kopec et al. 2007; Kessels and Malinow 2009; Kessels et al. 2009; Foster et al. 2010). Excitatory neurons preponderantly express the AMPAR GluN1/2 and GluN2/3 dimers (Wenthold 1996; Leuschner and Hoch 1999; Ayalon and Stern-Bach 2001; Kessels and Malinow 2009) and several heteromeric NMDAR (Luo et al. 1997; Hatton and Paoletti 2005; Paoletti and Neyton 2007; Paoletti 2011).

Inhibitory interneuronal functional properties, ranging from firing patterns to LTP rules, are different from those of excitatory cells (Zaitsev et al. 2005; Burkhalter 2008), and likely correlated with the receptor expression on interneurons (Moreau and Kullmann 2013).

We therefore set out to explore whether there are glutamate receptor patterns specific to inhibitory interneurons (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**). We

analysed the probability of expression of AMPAR subunits GluA1 through 4, as well as NMDAR GluN2A through D, independently for each subunit on each CBP-IR population. We found that there are two distinct expression profiles for glutamate receptors, which correlate with interneuronal firing patterns, as well as CBP expression. High GluA2 and GluA3 expression, low GluA1 and GluA4, as well as low overall GluN2 expression define the first expression profile, characteristic of PV-IR cells. In contrast, high GluA1, GluA4, as well as GluN2A through D, with low GluA2 and GluA3 characterize CB-IR and CR-IR cells (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**). This receptor expression division points towards different synaptic calcium influx for the two inhibitory interneuronal groups, which, combined with the different calcium buffering properties of the CBPs may give rise to their functional differences.

In the context of receptor expression, we tested the impact of AMPAR versus NMDAR blockers on early visual processing (Self et al. 2012; **Chapter V**). We assessed this for a figure-ground segregation task in macaque (Lamme 1995), in which the neuronal response pertaining to feed-forward and recurrent processing have been extensively characterised (Lamme 1995; Roelfsema et al. 2002; Super and Roelfsema 2005; Self et al. 2013; Van Kerkoerle et al. 2014). For this task, we found that the AMPAR blocker CNQX mostly affected feed-forward processing, while the generic NMDAR blocker APV reduced the difference between the figure and ground signals for recurrent processing. The majority of this impact is most likely due to blockage of excitatory activity. However, when investigating the GluN2B specific blocker Ifenprodil, we also observed reduced difference in recurrent processing, but with an overall increase of neuronal activity, suggesting GluN2B expression is related to inhibitory feedback (Self et al. 2012; **Chapter V**).

Thesis organization

This thesis is concerned with systematizing and clarifying layer organization of inhibitory interneurons, and characterising their expression of glutamate receptors, in macaque primary visual cortex.

Since the development of therapies for primates in rodent models assumes some degree of equivalence of cortical organization between the two, we first compared the expression of calcium binding proteins in primary visual cortex of mouse and macaque (**Chapter II**). Next, we explored the distribution of AMPA and NMDA glutamate receptor subunits on different classes of inhibitory cells, to understand the impact of excitatory inputs, and their integration, in interneurons (**Chapters III & IV**). Furthermore, we studied the impact of AMPA and NMDA receptor blockers in a complex visual task (**Chapter V**).

To address the points listed above, we conducted a series of anatomical and physiological experiments, using a variety of techniques. Importantly, we employed objective automated analysis for anatomical data, and provided numerous new insights into systematic mapping of interneurons.

The results are organised in scientific journal articles, some already published, and others currently in preparation, as indicated for each chapter.

References

Adesnik H, Bruns W, Taniguchi H, Huang ZJ, Scanziani M. 2012. A neural circuit for spatial summation in visual cortex. Nature. 490:226–231.

Applegate E. 2000. The Anatomy & Physiology Learning System. 2nd ed. Saunders.

Ascoli GA, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, Burkhalter A, Buzsaki G, Cauli B, DeFelipe J, Fairen A, Feldmeyer D, Fishell G, Fregnac Y, Freund TF, Gardner D, Gardner EP, Goldberg JH, Helmstaedter M, Hestrin S, Karube F, Kisvarday ZF, Lambolez B, Lewis DA, Marin O, Markram H, Munoz A, Packer A, Petersen CCH, Rockland KS, Rossier J, Rudy B, Somogyi P, Staiger JF, Tamas G, Thomson AM, Toledo-Rodriguez M, Wang Y, West DC, Yuste R, G PIN. 2008. Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci. 9:557–568.

Ayalon G, Stern-Bach Y. 2001. Functional assembly of AMPA and kainate receptors is mediated by several discrete protein-protein interactions. Neuron. 31:103–113.

Barinka F, Druga R. 2010. Calretinin expression in the mammalian neocortex: a review. Physiol Res. 59:665–677.

Barker LF. 1899. The Nervous System and its Constituent Neurones Designed for the use of practitioners of medicine and of students.

Bear MF, Malenka RC. 1994. Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol. 4:389–399.

Bliss T V, Collingridge GL. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 361:31–39.

Brodmann K. 1909. Vergleichende Lokalisationslehre des Grosshirninde in Ihren Prinzipien dargestellt auf Grund des Zellenbauen.

Bullock TH, Hagiwara S. 1957. Intracellular recording from the giant synapse of the squid. J Gen Physiol. 40:565–577.

Burkhalter A. 2008. Many specialists for suppressing cortical excitation. Front Neurosci. 2:155–167.

Callaway EM. 2004. Feedforward, feedback and inhibitory connections in primate visual cortex. Neural Netw. 17:625–632.

Campbell MJ, Lewis DA, Benoit R, Morrison JH. 1987. Regional heterogeneity in the distribution of somatostatin-28- and somatostatin-28(1-12)-immunoreactive profiles in monkey neocortex. J Neurosci. 7:1133–1144.

Carder RK. 1997. Immunocytochemical Characterization of AMPA-Selective Glutamate Receptor Subunits: Laminar and Compartmental Distribution in Macaque Striate Cortex. J Neurosci.

17:3352.

Carder RK, Hendry SH. 1994. Neuronal characterization, compartmental distribution, and activity-dependent regulation of glutamate immunoreactivity in adult monkey striate cortex. J Neurosci. 14:242–262.

Chard PS, Bleakman D, Christakos S, Fullmer CS, Miller RJ. 1993. Calcium buffering properties of calbindin D28k and parvalbumin in rat sensory neurones. J Physiol. 472:341–357.

Chatterton JE, Awobuluyi M, Premkumar LS, Takahashi H, Talantova M, Shin Y, Cui J, Tu S, Sevarino KA, Nakanishi N, Tong G, Lipton SA, Zhang D. 2002. Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. Nature. 415:793–798.

Clarke RJ, Johnson JW. 2006. NMDA receptor NR2 subunit dependence of the slow component of magnesium unblock. J Neurosci. 26:5825–5834.

Cole KS, Curtis HJ. 1939. Electric impedance of the squid giant axon during activity. J Gen Physiol. 22:649–670.

Conti F, Minelli A, DeBiasi S, Melone M. 1997. Neuronal and glial localization of NMDA receptors in the cerebral cortex. Mol Neurobiol. 14:1–18.

Cole KS, Curtis HJ. 1941. Membrane potential of the squid giant axon during current flow. J Gen Physiol. 24:551–563.

Cull-Candy SG, Leszkiewicz DN. 2004. Role of distinct NMDA receptor subtypes at central synapses. Sci STKE. 2004:re16.

Curtis HJ, Cole KS. 1938. Transverse electric impedance of the squid giant axon. J Gen Physiol. 21:757–765.

D'Orlando C, Celio MR, Schwaller B. 2002. Calretinin and calbindin D-28k, but not parvalbumin protect against glutamate-induced delayed excitotoxicity in transfected N18-RE 105 neuroblastoma-retina hybrid cells. Brain Res. 945:181–190.

DeFelipe J. 2010. Cajal's Butterflies of the Soul: Science and Art.

DeFelipe J, Jones EG. 1998. Cajal on the Cerebral Cortex - Santiago Ramon y Cajal - Oxford University Press.

DeFelipe J, López-Cruz PL, Benavides-Piccione R, Bielza C, Larrañaga P, Anderson S, Burkhalter A, Cauli B, Fairén A, Feldmeyer D, Fishell G, Fitzpatrick D, Freund TF, González-Burgos G, Hestrin S, Hill S, Hof PR, Huang J, Jones EG, Kawaguchi Y, Kisvárday Z, Kubota Y, Lewis D a, Marín O, Markram H, McBain CJ, Meyer HS, Monyer H, Nelson SB, Rockland K, Rossier J, Rubenstein JLR, Rudy B, Scanziani M, Shepherd GM, Sherwood CC, Staiger JF, Tamás G, Thomson A, Wang Y, Yuste R, Ascoli G a. 2013. New insights into the classification and nomenclature of cortical GABAergic interneurons. Nat Rev Neurosci.

14:202–216.

Dingledine R, Borges K, Bowie D, Traynelis SF. 1999. The glutamate receptor ion channels. Pharmacol Rev. 51:7–61.

Disney AA, Aoki C. 2008. Muscarinic acetylcholine receptors in macaque V1 are most frequently expressed by parvalbumin-immunoreactive neurons. J Comp Neurol. 507:1748–1762.

Erreger K, Geballe MT, Kristensen A, Chen PE, Hansen KB, Lee CJ, Yuan H, Le P, Lyuboslavsky PN, Micale N, Jorgensen L, Clausen RP, Wyllie DJ, Snyder JP, Traynelis SF. 2007. Subunit-specific agonist activity at NR2A-, NR2B-, NR2C-, and NR2D-containing N-methyl-D-aspartate glutamate receptors. Mol Pharmacol. 72:907–920.

Felleman DJ, Van Essen DC. 1991. Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex. 1:1–47.

Fino E, Packer AM, Yuste R. 2013. The logic of inhibitory connectivity in the neocortex. Neuroscientist. 19:228–237.

Foster K a, McLaughlin N, Edbauer D, Phillips M, Bolton A, Constantine-Paton M, Sheng M, Foster, Kelly A, Mc Laughlin, Nathan, Edbauer, Dieter, Phillips, Marnie, Bolton, Andrew, Constantine-Paton, Martha and Sheng M. 2010. Distinct roles of NR2A and NR2B cytoplasmic tails in long term potentiation. J Neurosci. 30:2676–2685.

Gonchar Y, Wang Q, Burkhalter A. 2007. Multiple distinct subtypes of GABAergic neurons in mouse visual cortex identified by triple immunostaining. Front Neuroanat. 1:3.

Grabarek Z. 2006. Structural basis for diversity of the EF-hand calcium-binding proteins. J Mol Biol. 359:509–525.

Härtig W, Brückner G, Brauer K, Seeger G, Bigl V. 1996. Triple immunofluorescence labelling of parvalbumin, calbindin-D (28k) and calretinin in rat and monkey brain. J Neurosci Methods. 67:89–95.

Hatton CJ, Paoletti P. 2005. Modulation of triheteromeric NMDA receptors by N-terminal domain ligands. Neuron. 46:261–274.

Hendry SH, Jones EG, Emson PC. 1984. Morphology, distribution, and synaptic relations of somatostatin- and neuropeptide Y-immunoreactive neurons in rat and monkey neocortex. J Neurosci. 4:2497–2517.

Henson MA, Roberts AC, Pérez-Otaño I, Philpot BD. 2010. Influence of the NR3A subunit on NMDA receptor functions. Prog Neurobiol. 91:23–37.

Hodgkin AL, Katz B. 1949. The effect of sodium ions on the electrical activity of giant axon of the squid. J Physiol.

Horridge GA. 1968. Interneurons: Their origin, action, specificity, growth, and plasticity.

Isaacson JSS, Scanziani M. 2011. How inhibition shapes cortical activity. Neuron. 72:231–243.

Jakab RL, Goldman-Rakic PS. 2000. Segregation of serotonin 5-HT2A and 5-HT3 receptors in inhibitory circuits of the primate cerebral cortex. J Comp Neurol. 417:337–348.

Jia Z, Agopyan N, Miu P, Xiong Z, Henderson J, Gerlai R, Taverna F a, Velumian A, Macdonald J, Carlen P, Abramow-newerly W, Roder J. 1996. Enhanced LTP in mice deficient in the AMPA receptor GluR2. Neuron. 17:945–956.

Jones EG. 1984. Neurogliaform or spiderweb cells. In: Peters A, Jones EG, editors. Cerebral cortex. New York: Plenum Press. p. 409–418.

Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ (Eds.). 2012. Principles of Neural Science. 5th ed.

Kessels HW, Kopec CD, Klein ME, Malinow R. 2009. Roles of stargazin and phosphorylation in the control of AMPA receptor subcellular distribution. Nat Neurosci. 12:888–896.

Kessels HW, Malinow R. 2009. Synaptic AMPA receptor plasticity and behaviour. Neuron. 61:340–350.

Kisvarday ZF, Cowey A, Somogyi P. 1986. Synaptic relationships of a type of GABA-immunoreactive neuron (clutch cell), spiny stellate cells and lateral geniculate nucleus afferents in layer IVC of the monkey striate cortex. Neuroscience. 19:741–761.

Kisvárday ZF, Gulyas A, Beroukas D, North JB, Chubb IW, Somogyi P. 1990. Synapses, axonal and dendritic patterns of GABA-immunoreactive neurons in human cerebral cortex. Brain. 113 (Pt 3):793–812.

Köhr G. 2006. NMDA receptor function: subunit composition versus spatial distribution. Cell Tissue Res. 326:439–446.

Kooijmans RN, Self MW, Beliën JAM, Wouterlood FG, Roelfsema PR. 2012. Two populations of inhibitory interneurons in macaque primary visual cortex express opposite glutamate receptor subunit combinations. In: SfN.

Kooijmans RN, Self MW, Wouterlood FG, Beliën JAM, Roelfsema PR. 2014. Inhibitory Interneuron Classes Express Complementary AMPA-Receptor Patterns in Macaque Primary Visual Cortex. J Neurosci. 34:6303–6315.

Kooijmans RN, Self MW, Wouterlood FG, Beliën JAM, Roelfsema PR. Parvalbumin immunoreactive cells show lowest NMDA receptor expression as compared to other inhibitory interneuron classes. In preparation.

Kooijmans RN, Sierhuis W, Self MW, Roelfsema PR. Laminar calcium-binding protein expression

in primary visual cortex of mouse and macaque. In preparation.

Kopec CD, Li B, Wei W, Boehm J, Malinow R. 2006. Glutamate receptor exocytosis and spine enlargement during chemically induced long-term potentiation. J Neurosci. 26:2000–2009.

Kopec CD, Real E, Kessels HW, Malinow R. 2007. GluR1 links structural and functional plasticity at excitatory synapses. J Neurosci. 27:13706–13718.

Kullmann DM, Asztely F, Walker MC. 2000. The role of mammalian ionotropic receptors in synaptic plasticity: LTP, LTD and epilepsy. Cell Mol Life Sci. 57:1551–1561.

Küppenbender KD, Standaert DG, Feuerstein TJ, Penney JB, Young AB, Landwehrmeyer GB. 2000. Expression of NMDA receptor subunit mRNAs in neurochemically identified projection and interneurons in the human striatum. J Comp Neurol. 419:407–421.

Lamme VA. 1995. The neurophysiology of figure-ground segregation in primary visual cortex. J Neurosci. 15:1605–1615.

Larkum ME, Nevian T, Sandler M, Polsky A, Schiller J. 2009. Synaptic integration in tuft dendrites of layer 5 pyramidal neurons: a new unifying principle. Science. 325:756–760.

Lee S, Hjerling-Leffler J, Zagha E, Fishell G, Rudy B. 2010. The largest group of superficial neocortical GABAergic interneurons expresses ionotropic serotonin receptors. J Neurosci. 30:16796–16808.

Lerma J, Morales M, Ibarz JM, Somohano F. 1994. Rectification properties and Ca2+ permeability of glutamate receptor channels in hippocampal cells. Eur J Neurosci. 6:1080–1088.

Leuschner WD, Hoch W. 1999. Subtype-specific assembly of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits is mediated by their n-terminal domains. J Biol Chem. 274:16907–16916.

Lewit-Bentley A, Réty S. 2000. EF-hand calcium-binding proteins. Curr Opin Struct Biol. 10:637–643.

Li W, Thier P, Wehrhahn C. 2001. Neuronal responses from beyond the classic receptive field in V1 of alert monkeys. Exp brain Res. 139:359–371.

Li Y., Ma W., Li L., Ibrahim L., Wang S., Tao HW. 2012. Broadening of Inhibitory Tuning Underlies Contrast-Dependent Sharpening of Orientation Selectivity in Mouse Visual Cortex. J Neurosci. 32:16466–16477.

Li Z. 2003. V1 mechanisms and some figure-ground and border effects. In: Journal of Physiology Paris. p. 503–515.

Luft FC. 2014. GABA the Hutt. J Mol Med (Berl). 92:551–553.

Lund JS. 1987. Local circuit neurons of macaque monkey striate cortex: I. Neurons of laminae 4C and 5A. J Comp Neurol. 257:60–92.

Lund JS. 1988. Anatomical organization of macaque monkey striate visual cortex. Annu Rev Neurosci. 11:253–288.

Lund JS, Hawken MJ, Parker AJ. 1988. Local circuit neurons of macaque monkey striate cortex: II. Neurons of laminae 5B and 6. J Comp Neurol. 276:1–29.

Lund JS, Wu CQ. 1997. Local circuit neurons of macaque monkey striate cortex: IV. Neurons of laminae 1-3A. J Comp Neurol. 384:109–126.

Lund JS, Yoshioka T. 1991. Local circuit neurons of macaque monkey striate cortex: III. Neurons of laminae 4B, 4A, and 3B. J Comp Neurol. 311:234–258.

Luo J, Wang Y, Yasuda RP, Dunah a W, Wolfe BB. 1997. The majority of N-methyl-D-aspartate receptor complexes in adult rat cerebral cortex contain at least three different subunits (NR1/NR2A/NR2B). Mol Pharmacol. 51:79–86.

Ma T, Wang C, Wang L, Zhou X, Tian M, Zhang Q, Zhang Y, Li J, Liu Z, Cai Y, Liu F, You Y, Chen C, Campbell K, Song H, Ma L, Rubenstein JL, Yang Z. 2013. Subcortical origins of human and monkey neocortical interneurons. Nat Neurosci. 16:1588–1597.

Mai JK, Paxinos G (Eds.). 2011. The Human Nervous System. 3rd ed.

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. 2004. Interneurons of the neocortical inhibitory system. Nat Rev Neurosci. 5:793–807.

Moreau AW, Kullmann DM. 2013. NMDA receptor-dependent function and plasticity in inhibitory circuits. Neuropharmacology. 74:23–31.

Nieuwenhuys R, Donkelaar HJ, Nicholson C. 1998. Mammals. In: The Central Nervous System of Vertebrates. Springer Science & Business Media.

Nieuwenhuys R, Voogd J, Huijzen C van. 2007. The Human Central Nervous System: A Synopsis and Atlas. Steinkopff.

Paoletti P. 2011. Molecular basis of NMDA receptor functional diversity. Eur J Neurosci. 33:1351–1365.

Paoletti P, Neyton J. 2007. NMDA receptor subunits: function and pharmacology. Curr Opin Pharmacol. 7:39–47.

Park H-J, Kong JJ, Kang YY, Park WW-M, Jeong SS, Park SS, Lim J-KJ, Jeon CC-J, Park J. 2002. The distribution and morphology of calbindin D28K- and calretinin-immunoreactive neurons in the visual cortex of mouse. Mol Cells. 14:143–149.

Pin JP, Duvoisin R. 1995. The metabotropic glutamate receptors: structure and functions. Neuropharmacology. 34:1–26.

Pin JP, Galvez T, Prézeau L. 2003. Evolution, structure, and activation mechanism of family 3/C G-protein-coupled receptors. Pharmacol Ther. 98:325–354.

Pinheiro Botelho E, Guimarães Martins Soares J, da Silva Pereira S, Fiorani M, Gattass R. 2006. Distribution of calbindin-28kD and parvalbumin in V1 in normal adult Cebus apella monkeys and in monkeys with retinal lesions. Brain Res. 1117:1–11.

Ramón y Cajal S. 1899a. Apuntes para el estudio estructural de la corteza visual del cerebro humano. Rev ibero-americana di ciencias medicas. 1:146–157.

Ramón y Cajal S. 1899b. Textura del sistema nervioso del hombre y los vertebratos. Madrid: Imprenta y libreria de Nicolas Moya.

Ramón y Cajal S. 1904. Textura del sistema nervioso del hombre y los vertebrados. Madrid: Imprienta y libreria de Nicolas Moya.

Rasch MJ, Schuch K, Logothetis NK, Maass W. 2011. Statistical comparison of spike responses to natural stimuli in monkey area V1 with simulated responses of a detailed laminar network model for a patch of V1. J Neurophysiol. 105:757–778.

Rockland KS. 1994. Primary Visual Cortex in Primates. Alan Peter. ed, Cerebral cortex. Springer.

Rockland KS, Pandya DN. 1979. Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. Brain Res. 179:3–20.

Roelfsema PR, Lamme VAF, Spekreijse H, Bosch H. 2002. Figure-ground segregation in a recurrent network architecture. J Cogn Neurosci. 14:525–537.

Rondard P, Pin J-P. 2015. Dynamics and modulation of metabotropic glutamate receptors. Curr Opin Pharmacol. 20:95–101.

Rossi AF, Desimone R, Ungerleider LG. 2001. Contextual modulation in primary visual cortex of macaques. J Neurosci. 21:1698–1709.

Rudy B, Fishell G, Lee S, Hjerling-Leffler J. 2011. Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. Dev Neurobiol. 71:45–61.

Schwaller B, Meyer M, Schiffmann S. 2002. “New” functions for “old” proteins: the role of the calcium-binding proteins calbindin D-28k, calretinin and parvalbumin, in cerebellar physiology. Studies with knockout mice. Cerebellum. 1:241–258.

Self MW, Kooijmans RN, Supèr H, Lamme VA, Roelfsema PR. 2012. Different glutamate receptors convey feedforward and recurrent processing in macaque V1. Proc Natl Acad Sci U S A. 109:11031–11036.

Self MW, Mookhoek A, Tjalma N, Roelfsema PR. 2015. Contextual effects on perceived contrast: figure-ground assignment and orientation contrast. J Vis. 15:2.

Self MW, van Kerkoerle T, Supèr H, Roelfsema PR. 2013. Distinct Roles of the Cortical Layers of Area V1 in Figure-Ground Segregation. Curr Biol.

Shanes AM. 1949. Electrical phenomena in nerve; squid giant axon. J Gen Physiol. 33:57–73.

Sherman SM. 2013. The Function of Metabotropic Glutamate Receptors in Thalamus and Cortex. Neuroscientist. 20:136–149.

Sherwood CC, Raghanti MA, Stimpson CD, Bonar CJ, de Sousa AA, Preuss TM, Hof PR. 2007. Scaling of inhibitory interneurons in areas v1 and v2 of anthropoid primates as revealed by calcium-binding protein immunohistochemistry. Brain Behav Evol. 69:176–195.

Shipton OA, Paulsen O. 2014. GluN2A and GluN2B subunit-containing NMDA receptors in hippocampal plasticity. Philos Trans R Soc Lond B Biol Sci. 369:20130163.

Siegelbaum SA, Kandel ER. 1991. Learning-related synaptic plasticity: LTP and LTD. Curr Opin Neurobiol. 1:113–120.

Standaert D, Landwehrmeyer G, Kerner J, Penney JJ, Young A. 1996. Expression of NMDAR2D glutamate receptor subunit mRNA in neurochemically identified interneurons in the rat neostriatum, neocortex and hippocampus. Brain Res Mol Brain Res. 42:89–102.

Super H, Roelfsema PR. 2005. Chronic multiunit recordings in behaving animals: advantages and limitations. In: VanPelt J, Kamermans M, Levelt CN, VanOoyen A, Ramakers GJA, Roelfsema PR, editors. Amsterdam: Elsevier Science Bv. p. 263–282.

Van Brederode JF, Mulligan K a, Hendrickson a E. 1990. Calcium-binding proteins as markers for subpopulations of GABAergic neurons in monkey striate cortex. J Comp Neurol. 298:1–22.

Van Kerkoerle T, Self MW, Dagnino B, Gariel-Mathis M-A, Poort J, Van der Togt C, Roelfsema PR. 2014. Alpha and gamma oscillations characterize feedback and feed- forward processing in monkey visual cortex. Proc Natl Acad Sci U S A.

Watakabe A, Komatsu Y, Sadakane O, Shimegi S, Takahata T, Higo N, Tochitani S, Hashikawa T, Naito T, Osaki H, Sakamoto H, Okamoto M, Ishikawa A, Hara S, Akasaki T, Sato H, Yamamori T. 2009. Enriched expression of serotonin 1B and 2A receptor genes in macaque visual cortex and their bidirectional modulatory effects on neuronal responses. Cereb Cortex. 19:1915–1928.

Wenthold R. 1996. Evidence for multiple AMPA receptor complexes in hippocampal CA1/CA2 neurons. J Neurosci. 16:1982–1989.

Witten IB, Knudsen EI. 2005. Why seeing is believing: merging auditory and visual worlds. Neuron. 48:489–496.

Zaitsev AV, Gonzalez-Burgos G, Povysheva N V, Kröner S, Lewis DA, Krimer LS. 2005. Localization of calcium-binding proteins in physiologically and morphologically characterized interneurons of monkey dorsolateral prefrontal cortex. Cereb Cortex. 15:1178–1186.